Neuropharmacology Drug Review

Antipsychotics

Classic (Typical) Antipsychotics - D_2 antagonists

Phenothiazines

- Chlorpromazine
- Fluphenazine - depot injection available
- Thioridazine – causes Torsades
- Trifluoperazine

Thioxanthenes

- Thiothixene

Butyrophenones - ↑ potency confers ↑↑ EPS

- Haloperidol (depot injection available)

Atypical Antipsychotic Agents - block D_{2C} and 5-HT_2 receptors

- Quetiapine – treats schizophrenia and acute manic episodes in bipolar disorder.
- Aripiprazole
- Clozapine - agranulocytosis and leukopenia (blood work required)
- Loxapine
- Risperidone – causes gynecomastia/galactorrea
- Olanzapine

The Atypical antipsychotics exhibit fewer EPS and fewer anticholinergic side effects.

Antidepressants

Tricyclic antidepressants - anticholinergic side effects

- Amitriptyline (nortriptyline is active metabolite) – used neuropathic pain
- Clomipramine – treats OCD
- Desipramine
- Imipramine (desipramine is active metabolite) – imipramine is used clinically to treat enuresis
- Nortriptyline

Selective serotonin reuptake inhibitors (SSRIs) - fewer anticholinergic side effects, less sedation and orthostatic hypotension

- Fluoxetine
- Paroxetine
- Sertraline
- Citalopram - QT prolongation and Torsade de Pointes, particularly at high doses
- Escitalopram

Monoamine oxidase inhibitors

Phenelzine – irreversible inhibitor of MAO-A and MAO-B
Tranylcypromine - irreversible inhibitor of MAO-A and MAO-B
Selegiline – MAO-B inhibitor, increases DA in synapse; adjunct with L-DOPA to treat Parkinson's Disease

Atypical Antidepressant Drugs

Bupropion – DA uptake blocker (Welbutrin ®, Zyban®)
Hypericum – extract of St. John's Wart
Mirtazapine – 5-HT2 and α2 (autoreceptor) antagonist
Trazodone – 5-HT uptake inhibitor (causes sedation and priapism)
Venlafaxine
Duloxetine

Mood Stabilizing Drugs

Lithium – inhibits formation of IP3; Used to treat the manic phase of bipolar disorder. Has a narrow therapeutic window, and overdose results in neurotoxicity and cardiac toxicity. Side effects include tremor, polyuria (vasopressin antagonist) and weight gain.
Quetiapine – atypical antipsychotic used to treat acute manic episodes in patients with bipolar disorder.
Carbamazepine –Na^+ channel blocker (alternative to lithium for bipolar disorder)
Valproate – Na^+ and Ca^{++} channel blocker (alternative to lithium for bipolar disorder)

Antiseizure Drugs

Phenytoin
Phenobarbital
Carbamazepine
Valproic Acid
Ethosuximide
Lamotrogine

Benzodiazepines

Drugs	Indications
Alprazolam	Anxiety, panic, phobias
Diazepam	Anxiety, preoperative sedation, muscle relaxation and withdrawal states
Lorazepam	Anxiety, preoperative sedation, status epilepticus (intravenous)
Midazolam	Preoperative sedation, anesthesia (intravenous)
Temazepam	Sleep disorders
Oxazepam	Sleep disorders, anxiety

Other Sedative-Hypnotics

zolpidem
zaleplon
eszopiclone - indicated for chronic treatment of insomnia
ramelteon

- activate the BZ1 site on GABAA-chloride ionophore, increasing chloride influx.
- do not significantly suppress slow wave or REM sleep.
- widely used to treat insomnia

Opiate Agonists and Antagonists

Strong Opiate Agonists

Morphine - prototype μ agonist
Oxycodone - used for breakthrough pain (postsurgical pain
Sufentanil - strong lipophilic μ agonist
Heroin – Prodrug (diacetylmorphine; not approved for medical use in the U.S.) P-450 inhibitors can induce withdrawal in opiate addicts.

Tramadol – μ opiate agonist plus 5-HT/NE uptake inhibitor – used to treat patients with neuropathic pain (post-herpetic neuralgia).

Moderate opiate agonists

Codeine (prodrug – methylmorphine) used to treat mild-moderate pain
Hydrocodone – combined with acetaminophen or NSAIDs

Other opiate agonists

Dextromethorphan – cough suppressant
Diphenoxylate- antidiarrheal agent (Lomotil®)
Loperamide - antidiarrheal agent (Imodium ®)

Mixed opioid agonist-antagonists –potent opiate analgesics in opiate-naïve patients. In patients who are physically dependent on opiates, these agents can precipitate withdrawal symptoms.

Buprenorphine
Butorphanol
Nalbuphine

Opioid antagonists

Naloxone – parenteral opiate antagonist
Naltrexone – orally available
Nalmefene - orally available

Tolerance, Dependence, and Withdrawal Symptoms

The chronic use of opioids can result in both tolerance (requiring escalating doses to achieve the same effect) and dependence. Withdrawal from chronic use can produce a variety of symptoms that may be severe:

Anxiety
Lacrimation
Rhinorrhea
Sweating
Yawning
Goose bumps
Hot or cold flashes
Muscle cramps and spasms
Gastrointestinal distress (vomiting and/or diarrhea)

Overview of Drug Therapy for Parkinson Disease

Drug	Mechanism of Action
Levodopa (L-DOPA)	Resolves dopamine deficiency by being converted to DA after crossing the blood-brain barrier
Dopamine agonists • Bromocriptine • Ropinirole	Directly stimulate dopamine receptors in basal ganglia
Anticholinergics • Benztropine (Cogentin) • Trihexyphenidyl (Artane)	Inhibit excessive acetylcholine influence caused by dopamine deficiency.
Amantadine	Unclear; may stimulate release of remaining dopamine or block effects of excitatory amino acids in the brain.
MAO inhibitors (MAOIs) Selegiline	Inhibits **MAO_B**, the enzyme that breaks down dopamine in the basal ganglia; enables dopamine to remain active for longer periods of time
COMT inhibitors Tolcapone, Entacapone	Help prevent breakdown of levodopa by catechol-O-methyl transferase (COMT) in peripheral tissues; allows more levodopa to reach the brain

L-DOPA → (**COMT**) → 3-0-methyldopa (blocked by tolcapone)
DA → (**MAO_B**) → DOPAC (blocked by selegiline)
DA → (**COMT**) → Homovanillic Acid (blocked by tolcapone)

Anesthesiology

Halothane -sensitizes myocardium to circulating catecholamines; **malignant hyperthermia**
Nitrous Oxide

[Succinylcholine also implicated in **malignant hyperthermia** – life-threatening syndrome consisting of severe muscle rigidity, hyperthermia, hypertension, acidosis and hyperkalemia]

Intravenous Anesthetics

Thiopental – short-acting barbiturate
Midazolam – short-acting benzodiazepine
Propofol - anesthetic used for relaxation before and during general for surgery or other medical procedure.
Fentanyl – μ opiate agonist
Ketamine – narcotic/dissociative anesthetic NMDA-receptor antagonist; Emergent delirium, hallucinations, cardiovascular stimulation